بسم الله الرحمن الرحيم

In The Name Of ALLAH

The Most Gracious, The Most Merciful

Armed Forces College of Medicine

AFCM

Treatment of Thyroid gland disorders

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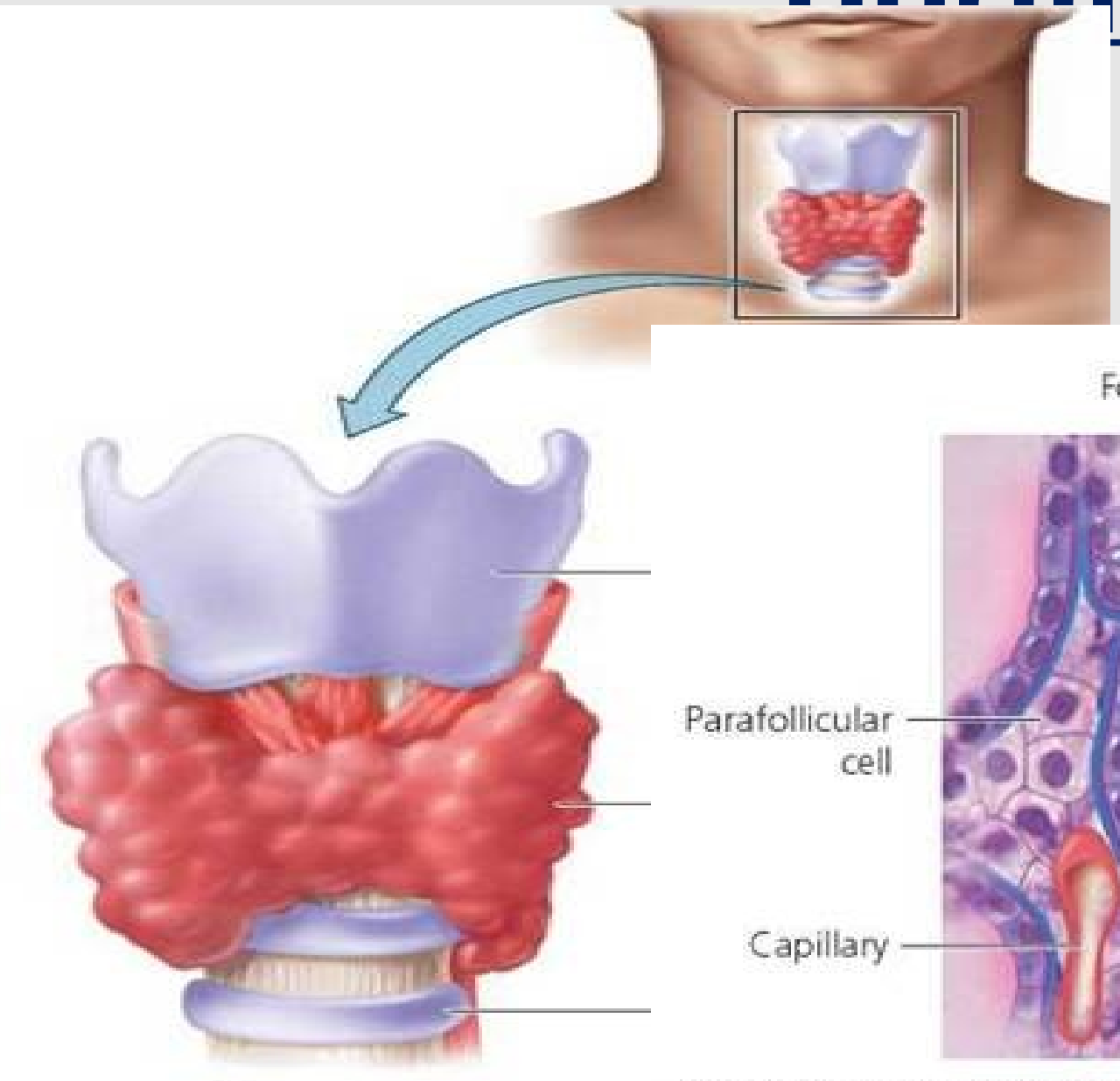
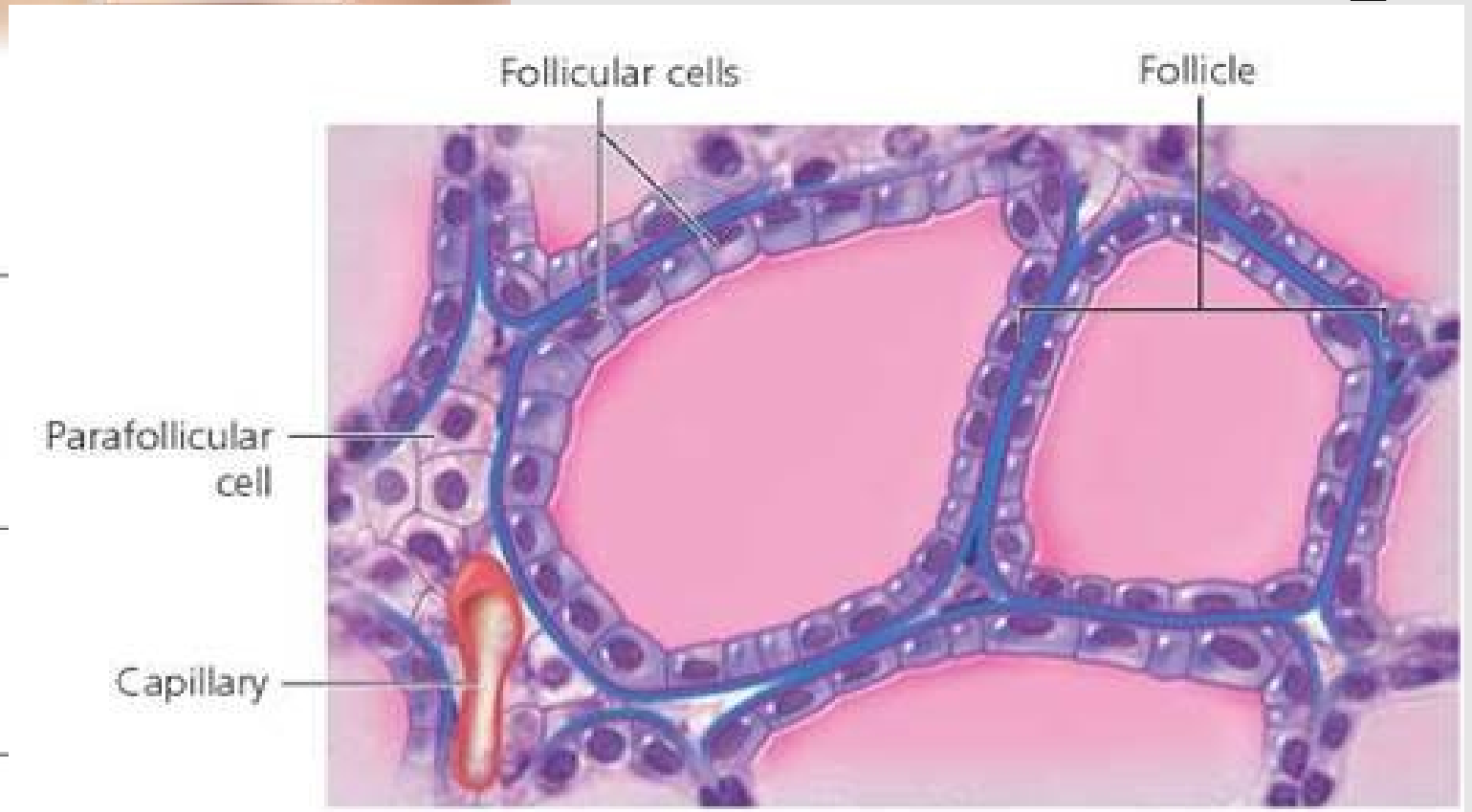
INTENDED LEARNING OBJECTIVES (ILO)

By the end of this lecture you will be able to:

1) List the drugs used in the treatment of hypothyroidism
2) Compare between Liothyronine& Levothyroxine
3) Outline a plane of therapeutic managment of myxoedema coma
4) List the drugs used in the treatment of hyperthyroidism.
5) Describe the mechanism of action of the antithyroid drugs
6) Explain the adverse effects of antithyroid drugs
7) outline a plane of therapeutic managment of Thyroid crisis (storm)

Thyroid Hormones





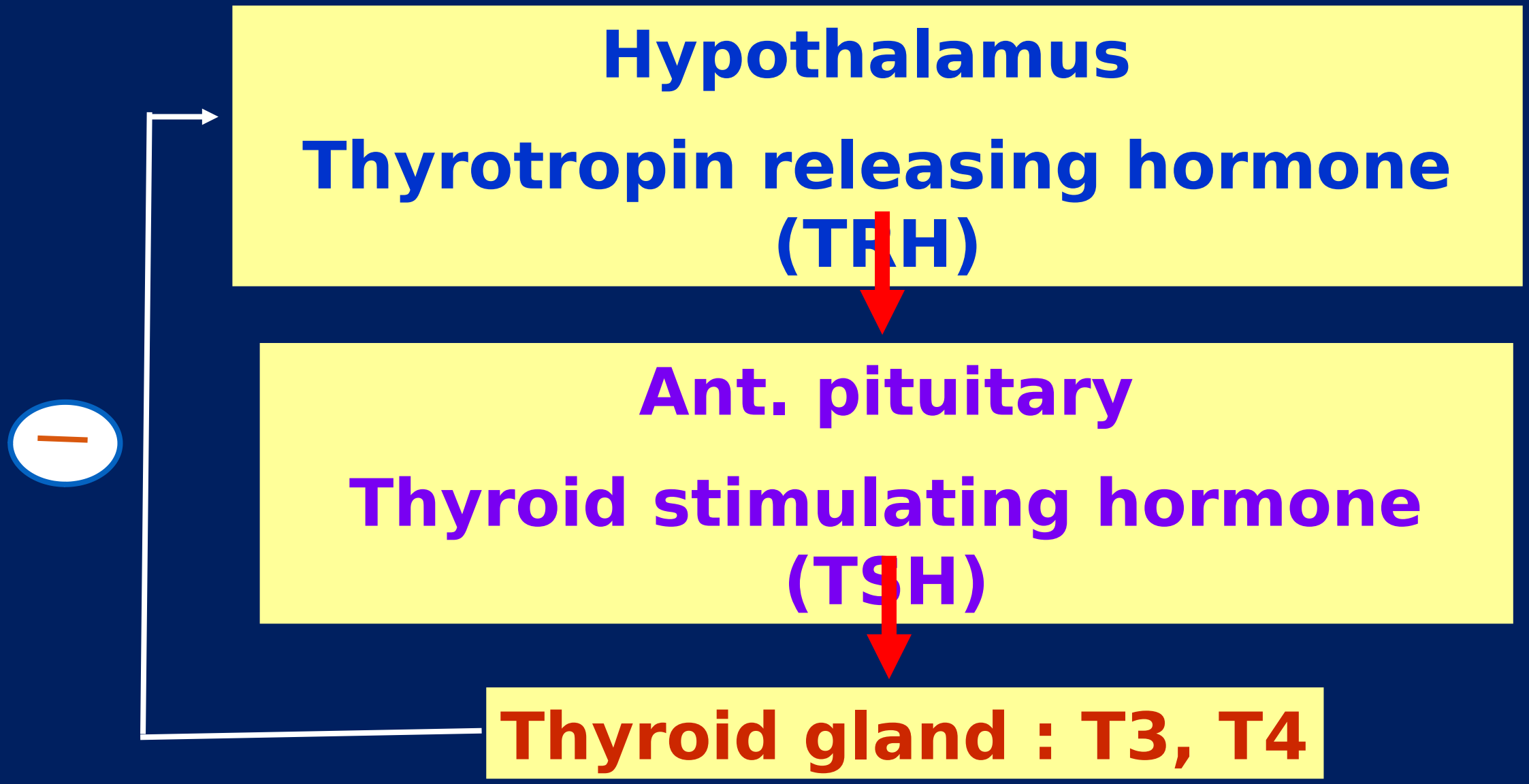
Thyroid gland synthesizes

- From follicels T_3 , T_4
- Parafollicular cells Calcitoni

Thyroid Disorders

- **Hypothyroidism** results in:
  Bradycardia, cold intolerance, mental and physical slowing,
  weight gain
  In adults: Myxedema
  In children : **Cretinism** ⇨ result in mental retardation & dwarfism .

- **Hyperthyrodism** results in:
  Tachycardia & cardiac arrhythmia, heat


Hypothalamus
Thyrotropin releasing hormone
(TRH)
Ant. pituitary
Thyroid stimulating hormone
(TSH)
Thyroid gland : T3, T4
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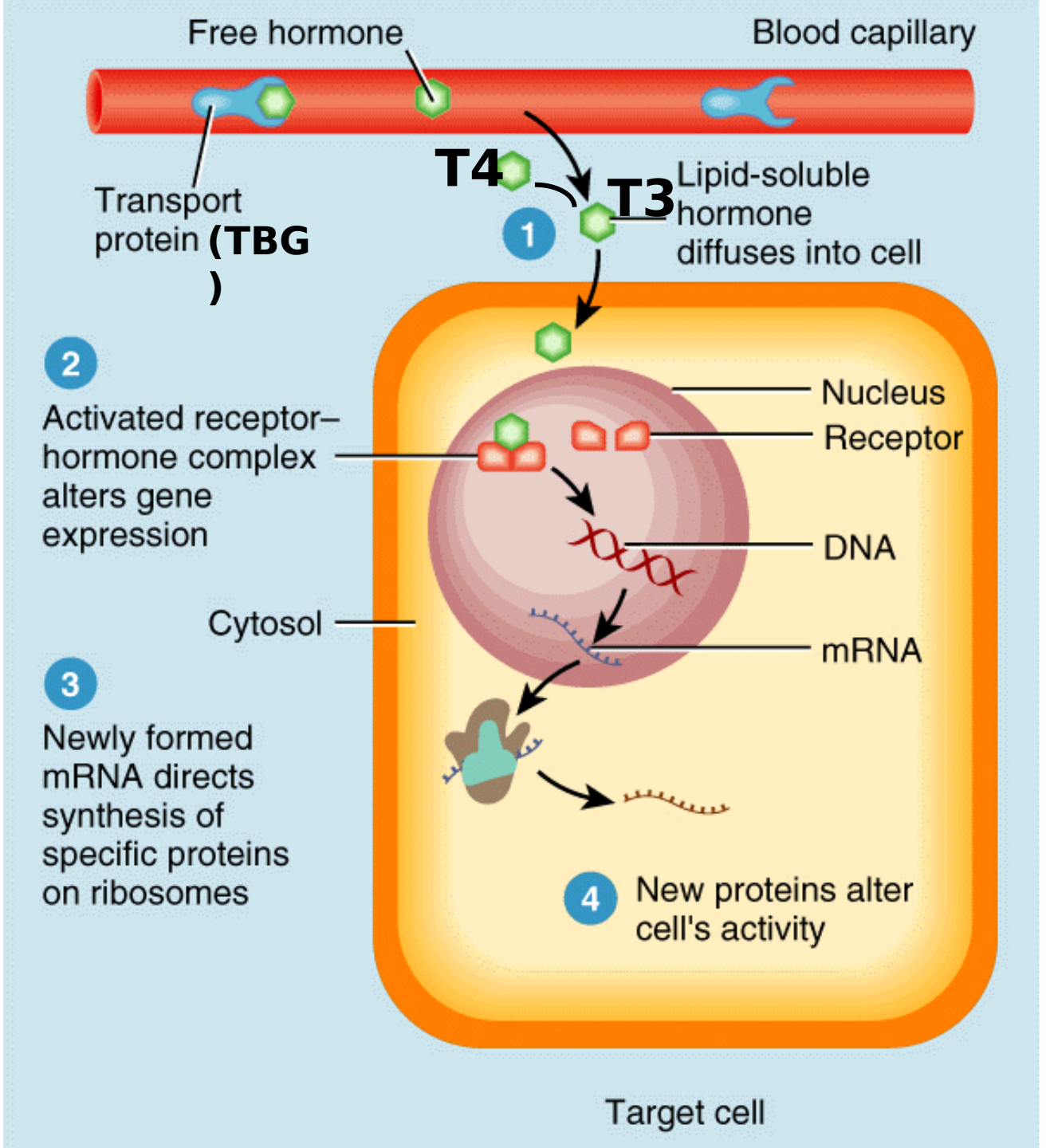
Mechanism of action

- T3 and T4 dissociate from Thyroxin binding globulin (TBG) and enter cells by diffusion or active transport
- Inside the cell:

  T4 deiodinated to T3
- T3 enters the nucleus and attaches to its receptor
- Drug- receptor complex bind to DNA and promote gene transcription→ RNA formation→ protein synthesis (enzymes)



Pharmacokinetics

Absorption:

Oral: T3 and T4 are absorbed

food, antacids, Ca product ↓ absorption of T4

Metabolism:

- **T4 is converted to T3 by deiodinases** depending on the tissues (40% is converted to inactive rT3)
- **Metabolized by p450**

enzyme inducers ↑ metabolism of thyroid hormones

Excretion:

Partly in bile & Partly in urine.

Treatment of hypothyroidism

- T_4 (levothyroxine).
- GIVEN ONCE DAILY, LONG $T_{1/2}$
- Steady state is reached in 6-8 weeks
- Toxicity: nervousness, palpitations, tachycardia, heat intolerance, weight loss

Thyroid Hormone Preparations

Levothyroxine (T4)	**Liothyronine (T3)**
Stable and low cost	Stable but higher cost
Long $t_{1/2}$ (7days) Given once daily	Shorter $t_{1/2}$ (24h) Multiple daily doses
Less risk of cardiotoxicity	**Greater risk** of cardiotoxicity

Thyroid Hormone Replacement during Pregnancy

A higher dose of L-T4 often is required in hypothyroid pregnant (typically 25–40% over basal).

Myxoedema Coma

- Extreme expression of severe hypothyroidism.
- An emergency.

I.V therapy (impaired absorption of drugs fom other routes)

1. **Loading dose of I.V levothyroxine**
   (usually loading dose of 300–400 mcg initially, followed by 50–100 mcg daily.)
   OR Liothyronine (T3) I.V
   (5–20 mcg initially, followed by 2.5–10 mcg every 8 hours)
   but may be more **cardiotoxic and more difficult to monitor.**

   These patients have large pools of empty T3 and T4 binding sites that must be filled before there is adequate free thyroxine to affect tissue metabolism.
2. **Hydrocortisone** I.V. (if adrenal or pituitary insufficiency is present).

   Because of the possibility of secondary hypothyroidism and associated hypopituitarism, hydrocortisone should be administered until adrenal insufficiency has been ruled out. In

Hyperthyrodism (thyrotoxicosis)

Is manifested by increased metabolic rate, intolerance to heat, weight loss with increased appetite, nervousness, tachycardia, anginal Pains, fatiguability, muscle weakness, -ve nitrogen balance and osteoporosis.

Exophthalmos is present in Graves`s disease.

Treatment of hyperthyroidism

- Grave's, toxic adenoma and multinodular goiter
- Goal of therapy:
  ↓ synthesis and/or release of thyroid hormones
- **Surgical**
- **Radioactive iodine (I^{131})**: selectively taken by thyroid follicle cells
- **Medical:**

1. Thioamides: Propylthiouracil, Carbimazole & Methimazole

2. Iodide: K iodide, Lugol's iodine

Thioamides (Thiourea Derivatives)

1-Carbimazole (prodrug).

2- Methimazole is the active metabolite of Carbimazole

3- Propylthiouracil (PTU)

Propylthiouracil:

- acts more **rapid:**
  (prevents conversion of T4 toT3 in peripheral tissues)

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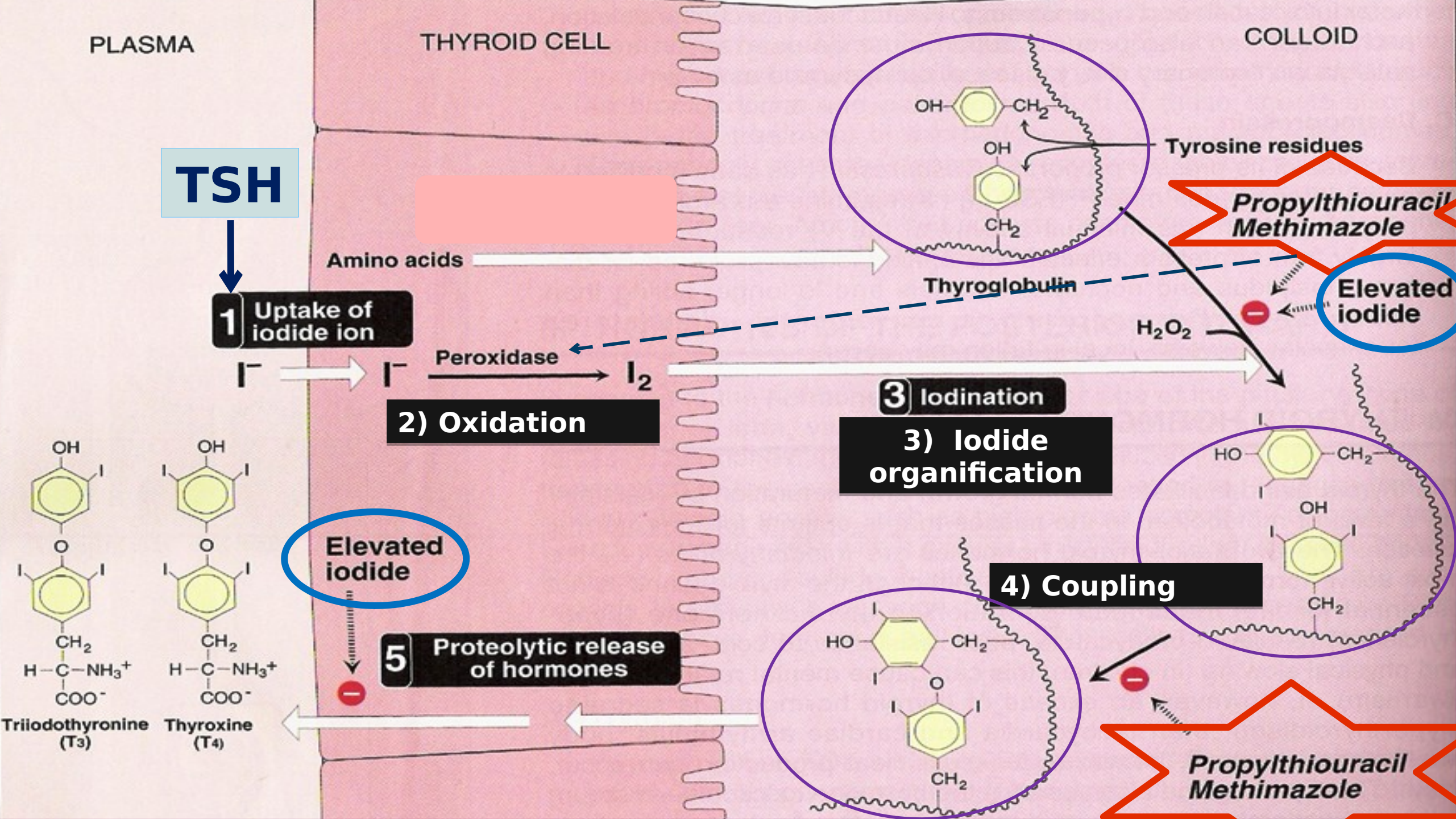
PLASMA
THYROID CELL
COLLOID
TSH
Amino acids
1 Uptake of iodide ion
I^-
I^-
Peroxidase
I_2
2) Oxidation
OH
CH_2
OH
CH_2
Tyrosine residues
Propylthiouracil
Methimazole
Thyroglobulin
H_2O_2
Elevated iodide
3 Iodination
3) Iodide organification
HO
CH_2
OH
CH_2
4) Coupling
HO
CH_2
O
CH_2
Propylthiouracil
Methimazole
Elevated iodide
5 Proteolytic release of hormones
OH
O
CH_2
$H-C-NH_3^+$
COO^-
Triiodothyronine (T_3)
OH
O
CH_2
$H-C-NH_3^+$
COO^-
Thyroxine (T_4)

Thioamides

Mechanism of action:

Inhibit synthesis of thyroid hormones

1. Inhibition of **oxidation** of iodide to iodine.
2. inhibit the **iodination** of tyrosine
3. inhibit **coupling** of iodotyrosines to form T_3 and T_4
4. **PTU** block the conversion of $T_4 \rightarrow T_3$

Effect delayed until thyroglobulin stores are depleted

Slow effect,

NOT EFFECTIVE IN CONTROLLING THYROID STORM **ALONE**

Thioamides

Therapeutic uses: -

Treatment of hyperthyroidism:

1) as principal therapy.

2) as adjuvant to I^{131} to control the disease until radiation achieves its effect.

3) to prepare (control the disease) the patient for surgery.

4) Thyroid storm (PTU inhibits conversion of T4 to T3)

5) In pregnancy:

Both propylthiouracil and methimazole cross the placenta equally,

However, Methimazole is usually AVOIDED in the first trimester and Propylthiouracil is preferred due to methimazole-associated embryopathy,

and then methimazole is used for the remainder of the Pregnancy due to

Thioamides

Adverse effects:

Most common: rash

Most dangerous but Rare & reversible: agranulocytosis

Hepatitis, cholestatic jaundice

Loss of hair, abnormal hair pigmentation

Iodide therapy

Mechanism of action:

1. Inhibits iodide organification
2. Inhibits the release of thyroid hormones
3. ↓ size and vascularity of thyroid gland

Uses: Given orally (KI , Lugol's iodine)

- Rarely used as monotherapy
- Response ↓ with time (in 10 – 14 days)
- Used in thyroid storm and preoperative

Adverse effects:

Rashes, angioedema, Sore mouth and throat, ulcerations of mucus membrane, metallic taste

Radioactive iodine I^{131}

- **Given orally**

  Concentrated in the thyroid gland ,

  it Emit β & γ rays that destroy thyroid parenchyma

- **Therapeutic uses:-**

  1- Hyperthyroidism. (adults > 45 years & in patient not fit to surgery)

  recurrence after medical or surgical treatment

  2- Thyroid cancer.

- **The action appears after 1-2 months and becomes**

Radioactive iodine I^{131}

Side effects:

1- Hypothyroidism (The chief toxic effect).

2- Thyroid storm (release of thyroid hormone).

3- Patient may require repeated doses.

4- Leukemia.

5- Slow onset .

Contraindications: -

1- Young age

2- Pregnancy (crosses placenta) & lactation (excreted in milk).

Thyroid crisis (storm)

- **Beta blockers** IV without sympathomimetics activity (propranolol):
  - Control CVS symptoms
  - Prevent conversion of T_4 to T_3
  - ***If BB is contraindicated diltiazem can be used***
- **Hydrocortisone IV** : protect against shock &Prevent conversion of T_4 to T_3
- **PTU or methimazole** to block hormone synthesis
- **K iodide** to inhibit release of thyroid hormones

Quiz

All of the following actions are caused by propylthiouracil EXCEPT:

a) Decrease of iodide uptake by the gland

b) Block of coupling of iodotyrosines to form T3 & T4

c) Block of iodination of tyrosyl residues in thyroglobulin to form monoiodotyrosine.

d) Inhibition of transformation of T4 to T3

Quiz

Which of the following statements is **WRONG:**

a) Carbimazole is used in ttt of hyperthyroidism
b) Levothyroxine is used in ttt of hypothyroidism
c) Methimazole is metabolized into carbimazole
d) Propylthiouracil can be used during pregnancy
e) Agranulocytsis is a side effect of carbimazole

Quiz

All the following about Levothyroxine (T4) are correct EXCEPT:

a) Long t ½
b) Given once daily
c) Stable
d) Greater risk of cardiotoxicity than Liothyronine (T3)

SUGGESTED TEXTBOOKS

1. Whalen, K., Finkel, R., & Panavelil, T. A. (2018) Lippincott's Illustrated Reviews: Pharmacology (7th edition.). Philadelphia: Wolters Kluwer

2. Katzung BG, Trevor AJ. (2018). Basic & Clinical Pharmacology (14th edition) New York: McGraw-Hill Medical.


Thank You!